Application Reviews by RFA/Genomics/GC1R-06709

REVIEW REPORT FOR CIRM RFA 12-06R GENOMICS CENTERS OF EXCELLENCE AWARDS (R)

GC1R-06709: Center for Advanced Stem Cell Genomics

GWG Overall Center Recommendation: Tier 1
GWG Overall Final Score: 76

GWG Data Center Recommendation: Tier 2
GWG Data Center Final Score: 72

CIRM Staff Recommendation: Do not fund

Public Abstract (provided by applicant)
Genomics is the study of our DNA sequences, how certain genes become active and inactive during human development, how different cells express their unique identities. Dysfunction in genes causes inherited diseases and cancer. The goal of the Center for Advanced Stem Cell Genomics is to study the genomics of human stem cells, to understand how they develop into specific cell types that are valuable for cell therapy, drug development, and for study of human diseases. The Center is a partnership between an academic pioneer in stem cell genomics research and research scientists at the world's leading genomics tools and services company. Our primary mission is to vitalize the power of stem cells to improve human health by providing genomics tools, such as DNA sequencing, epigenetic analysis, and gene expression analysis, to the stem cell community in California and to CIRM's US and international funding partners. The Center will have tremendous impact on the field of stem cell research and clinical uses worldwide, greatly raising our level of understanding of stem cells and enabling their potential to cure human disease.

Statement of Benefit to California (provided by applicant)
California has had remarkable success in spawning biotechnology companies. Since Genentech was founded in 1976, biotechnology has taken on a distinctly California flavor, and ingenuity and entrepreneurship have thrived in the state for the last 30 years. Currently there are more than 2,000 biomedical companies in California, employing more than 250,000 people, with estimated revenue of $115 billion. Salaries for biotechnology company employees total more than $20 billion each year. Biotechnology bridges the gap between basic and applied research, encouraging new inventions and inspiring a well-educated workforce. After CIRM was founded in 2004, their investments in human stem cell research have made California the most productive site for the stem cell research in the world. These two California-born ideas are brought together by CIRM's proposal for Stem Cell Genomics Centers of Excellence Awards. Only in California could stem cell researchers partner with the genomics industry to push forward the progress toward regenerative medicine and more efficient drug development. The Centers will spawn a new California specialty that will bring new jobs and improve human health - the best of both worlds.

Review Summary

This Genomics Center will be led by a program director (PD) from an academic institution and a co-PD from an industry organization. Three Center-Initiated Projects (CIPs) are proposed, and, as required by the RFA, a plan for inclusion of Collaborative Research Projects and a Data Coordination and Management Center are described.

Center Organization and Operational Plan

- The organization of the proposed Genomics Center is well conceived as a collaboration between highly qualified investigators from an academic institution and an industry partner, representing a diversity of competencies. The balance between expertise in stem cell biology and genomics technologies is a particular strength.

- The PD has extensive research experience at the interface of stem cell biology and genomics and is committed to serving the stem cell community; he/she is well suited to lead this program.

- The industry partner institution, and especially the co-PD, is well positioned to develop novel cutting edge genomics technologies and make them accessible to customers.

- The teams from the two applicant institutions have a well-established, strong working relationship; reviewers considered this an important attribute of this proposal.

- All elements necessary for the establishment and operation of a successful Genomics Center are in place; the structure and composition of the proposed administrative and oversight committees are appropriate and should ensure both delivery of projects and high standards of work.

- The three CIPs are designed to support the service aspects of this Genomics Center by focusing on the development of tools that can be generally used to explore genomics data. Reviewers considered it a strength that, if successful, these projects will both create novel tools and technologies and validate them. There was some concern that some of the tools may not be made easily and widely available.

- Although a letter from leadership indicates enthusiastic institutional support from the academic institution, no additional funds or specific dedicated space have been designated. Reviewers expressed serious concern about this lack of material commitment.

- Some reviewers expressed concern that both the PD and co-PD are already heavily committed individuals and questioned whether they would have the capacity to fully provide a strong commitment to this project.

Collaborative Research Projects

- The proposed Genomics Center appears well designed to support collaborative research projects and to make relevant state-of-the-art genomics technologies readily accessible to investigators with primary expertise in stem cell biology or translational research.

- The proposed application process is appropriate, review procedures and criteria are well thought out.

- The offer to culture cells for external collaborators in the Genomics Center's core lab is especially appealing, as that would remove a variable from the experiments and thus help with standardization of conditions for genomics assays.

- Concern was expressed about whether potential collaborators who have limited experience in genomics would receive adequate assistance in designing their proposed studies.

CIP-1

The applicants propose to develop an updated and expanded version of an existing genomics tool. They plan to make available global gene expression and epigenomic data, obtained through a series of systematic analyses of human pluripotent stem cells and their derivatives, to serve as reference for future experiments. They also propose to analyze the heterogeneity of stem cell populations and to develop genomic tools for the assessment of stem cell quality. Finally, they intend to use disease-specific induced pluripotent stem cells (iPSC) to study the molecular basis of two neurodevelopmental diseases and identify disease-modifying compounds.

- This project adopts a broad approach toward developing pragmatic, accessible tools for basic research on stem cells in vitro, and to lay the groundwork for more effective clinical translation. This would represent a valuable resource to the stem cell community.

- Enthusiasm was diminished by the notion that most of the activities are applications of existing tools or extensions of existing work. While important goals, the activities were not viewed as particularly innovative.

- The goals of this project are overly ambitious, raising doubt that all aims can be achieved. Given the tremendous track record of the principal investigator (PI), though, it is expected that substantial progress will be made.

- Reviewers' opinions about the utility of an already existing analytical tool, to be further developed under this award, were divided. Some judged it positively as an important tool that has been made freely available in its current form and were enthusiastic about the plan for dissemination of the updated version. Conceptually, they considered the proposed approach to be very valuable, as it has the potential to provide objective standards for assessing cell fate and for quality control of cell populations. Other reviewers expressed concern that the current tool has not been widely adopted in the stem cell community, calling into question its usefulness.

- The proposed work on neurodevelopmental diseases is disconnected from the central focus of this project and might have been better developed as a separate project.

- Reviewers criticized the general lack of experimental detail, particularly in aims 4 and 5, which impeded assessment of feasibility.

- The project plays to the strengths of the PI as a well-established leader in the stem cell field with a strong record of productivity and innovation.

- The broad scope of the project is matched by the experience and expertise of the team involved.

CIP-2

This project addresses the integrity of stem cells for clinical transplantations and their utility in translational and clinical research. The goals are to establish informatics tools for determining the functional significance of genome wide molecular variations in therapeutic stem cell populations and to develop and validate methods for assessing the prevalence of deleterious alterations in stem cell populations. The applicants also plan to develop and validate a workflow for integrating genomics information with identification of potential therapeutic compounds and their effects on patient-derived induced pluripotent stem cells and on patient treatment outcomes. Finally, the plan is to disseminate all developed tools and protocols to the stem cell community.

- The utility of the proposed tools and protocols for translational genomics-based research would be high.

- The first goal is straightforward and feasible. Reviewers emphasized that input data must be high quality, as noted by the applicants, and suggested that applicants consider that the cellular differentiation state may affect functional significance of specific genomics variation.

- Other goals are more risky, but if successfully developed, they should be widely applicable and help stimulate the use of stem cell-based systems to explore both disease mechanisms and potential therapies.

- Toward assessing prevalence of deleterious alterations in stem cell populations, reviewers recommended that a variety of additional stem cell datasets, especially some originating outside the team, be included in the project.

- The feasibility of a key component of the study, linking genomic information from patients to potential therapeutics and individualized treatments, was difficult to assess, since the applicants did not specify the types of diseases to be studied.

- Reviewers observed that parts of this proposal are vague and hard to follow, and it was unclear what some of the deliverables would be.

- There is a clear plan for dissemination of the acquired expertise and knowledge.

- The PI is well qualified for this work and has assembled a powerful leadership team that possesses the necessary expertise.

CIP-3

This project is led by the industry partner organization and is focused on the development of several single cell genomic technologies and tools for large-scale epigenetic analyses.

- Reviewers noted that only one of the technologies under development is truly stem cell-specific, but the proposed work would nevertheless deliver technologies extremely valuable to the stem cell community.

- The tools to be improved or developed are at the forefront of technical advances.

- Reviewers geatly appreciated the novelty of one of the proposed technologies.

- Some reviewers were concerned that the project essentially constitutes commercial development of genomic products and questioned whether it was appropriate for CIRM to support this activity. Others felt that the developed technologies would provide valuable research tools and could have great potential impact on stem cell science.

- Concern was expressed about whether the new technologies would be specifically disseminated to California investigators and whether their cost might be prohibitive to many researchers.

- The basic technologies underlying this proposal have already been developed and it should therefore be feasible to complete the

proposed developments in the proposed time scale.

- The PI and team are exceptionally well qualified to deliver on this project.

Data Coordination and Management

- The DCM team is led by two individuals. One has a track record of developing a highly successful, adaptable, user-friendly platform. The other is an expert in medical informatics, although reviewers expressed concern that a biosketch for this individual was not included in the proposal.

-The proposed DCM structure and leadership would likely ensure solid database structure, data access and visualization capabilities.

- Reviewers considered the details provided on the data management plan to be inadequate; there was little description of how the DCM Center will participate in data integration and analysis or interact with various projects.

- Reviewers acknowledged the importance of patient privacy protection but felt the focus on this issue in the application was overemphasized and distracting.

- The descriptions of data visualization tools are reasonable but not particularly innovative or tailored to the specific needs of the stem cell community.

Conflicts

- Maynard Olson
- Martin Pera
- Jared Roach
